Tuberculosis in the US Military

Edward Munch.

The Sick Child. **(1885)**

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Slides by: LTC James Mancuso

Outline

- Active vs. Latent TB
- Active TB diagnosis and treatment
- LTBI diagnosis and treatment
- Military screening policies
- Other issues

TB Trivia 1

Case Study

- SPC Snuffy, a 24 year old male Soldier, comes in after a 12 month deployment with the 101st. His paperwork says "positive PPD."
  - What more do you want to know from the history?
  - What does the PPD mean?
  - Other tests necessary?

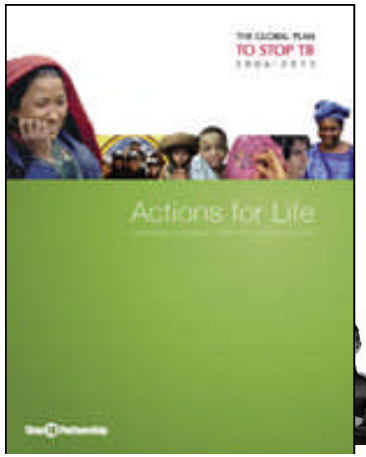
Evaluation of SPC Snuffy

- Symptoms? → Sputum X 3
- Exposure?
  - Foreign born?
  - Contact with known **ACTIVE** TB case?
  - Other risk factors? (Occupation, activities, medical history)
- PPD?
  - How many mm?
  - Previous positive (or previous 9 mm RXN)?
  - Previous BCG vaccine?
  - Use of Quantiferon Gold-in-tube or T-SPOT.TB?
- CXR?
- Treatment?

TB Trivia 2

Global Burden of Tuberculosis

- 9.2 million cases and 1.7 million deaths yearly
- Associated with co-pandemic of HIV
- Drug-resistance increasingly common
- 1/3 of the world's population estimated to be infected with LTBI
  - Focus on identification and treatment of active TB (DOTS)
  - LTBI not a well-known concept outside the US
  - Increasing efforts to extend LTBI treatment to HIV populations



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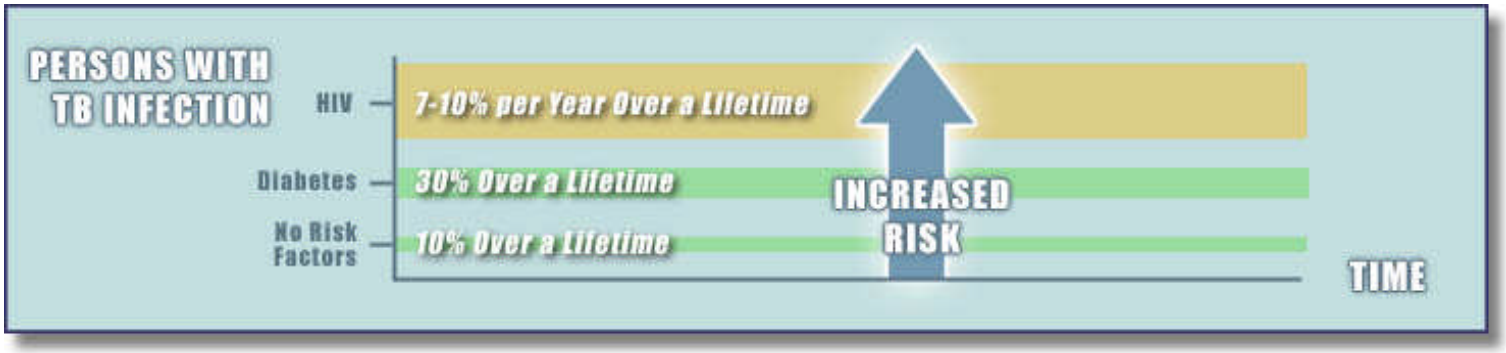
Low-stress test: Question 1

- Which of the following forms of TB is/are considered infectious from person-to-person?

a) Latent TB infection (LTBI)
b) Active TB—Pulmonary
c) Active TB—Lymphatic
d) Active TB—Laryngeal

TB Pathophysiology

- Spread person-to-person through the air
- Droplet nuclei may remain in the air
- Primary infection
  - Inhale tubercle bacilli
  - Reach alveoli, engulfed by macrophages
  - Some multiply intracellularly and released
  - Immune system (cell-mediated) prevents progression
- Activation
  - Tubercle bacilli overcome immune system
  - “5% risk in 2 years, 10% lifetime”



Active TB

- Chronic granulomatous infection caused by *M. tuberculosis* complex
- Contagious
- Lung disease is the most common manifestation (80%)
- Extrapulmonary (20%)
  - Lymphadenitis (scrofula)
  - Meningitis

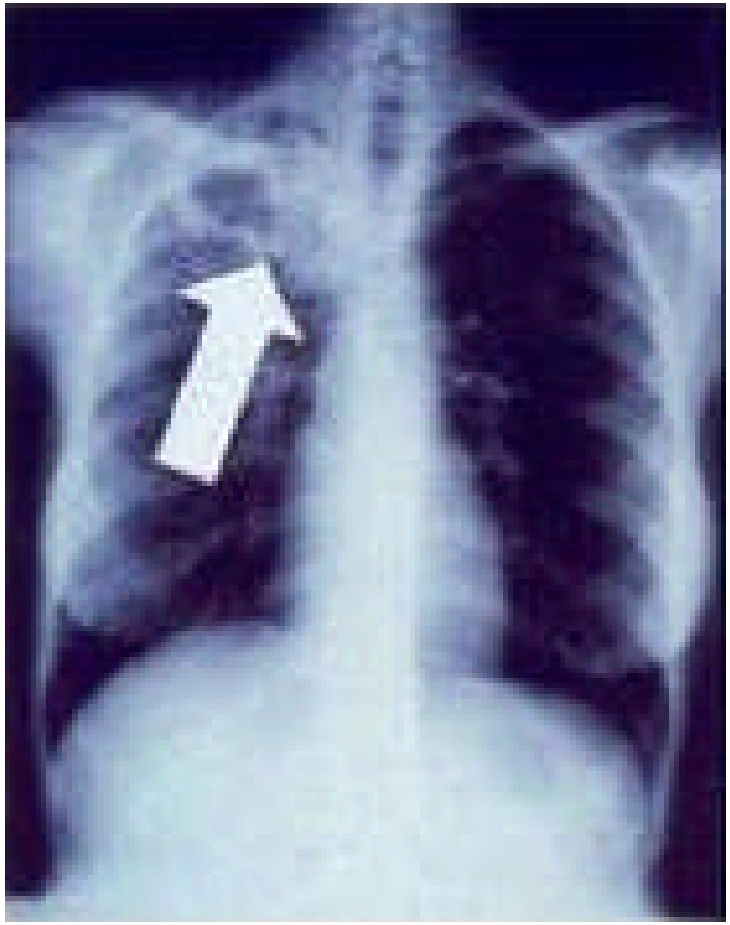
Diagnosis of TB

- Clinical symptoms and signs
- CXR (not confirmatory)
- Sputum smear (AFB) (sensitivity 50%)
- Culture
- NAATs
- Sensitivity testing

Symptoms of TB

- Fever
- Chronic cough
- Night sweats
- Hemoptysis
- Weight loss (unplanned)
- Fatigue

CXR



AFB Smear

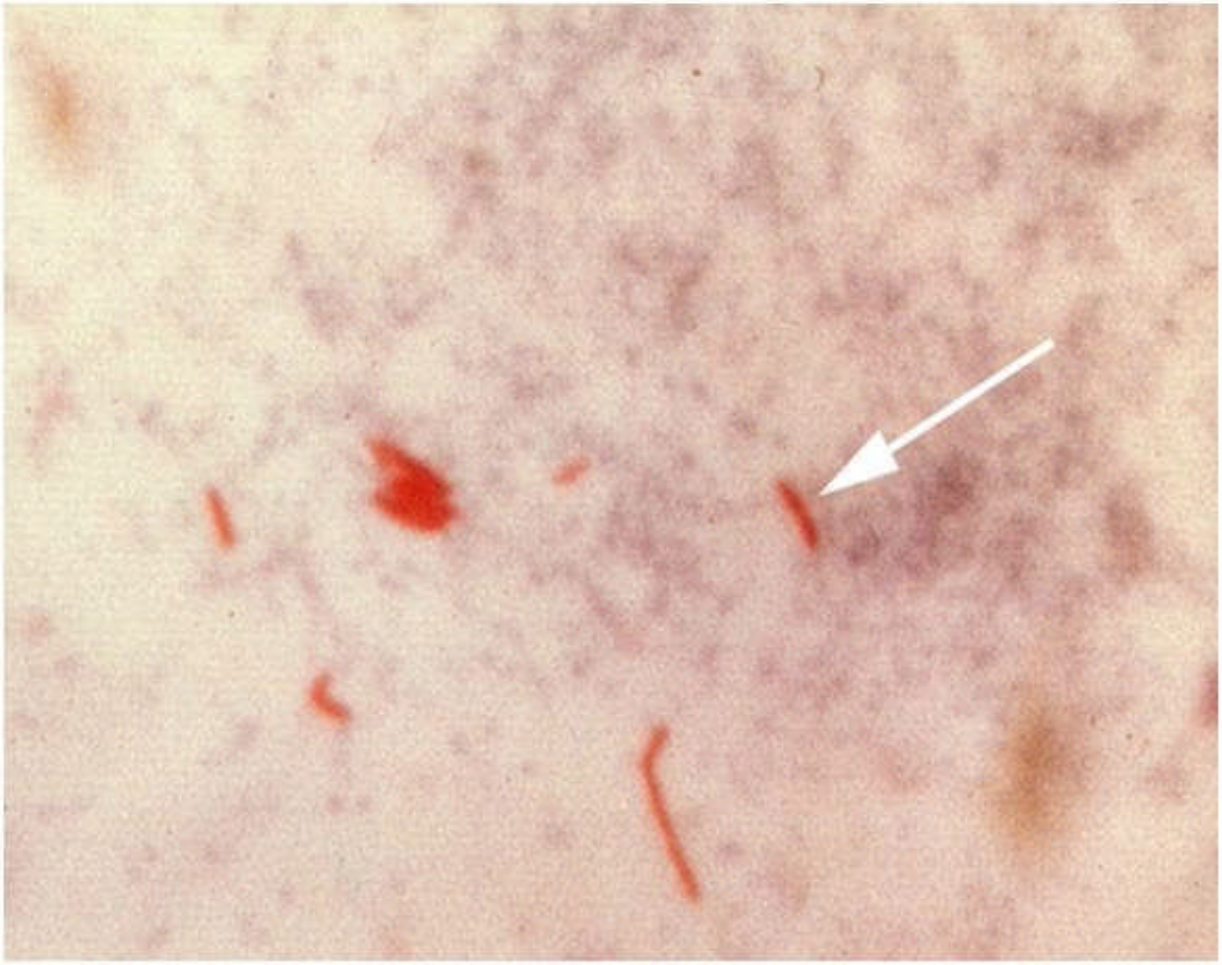


Figure 9. Sputum specimen demonstrating acid fast bacilli (AFB) (arrow). Source CDC.

Treatment

- “4 for 2 and 2 for 4”
  - INH, RIF, PYR, EMB X 2 months
  - INH, RIF X 4 months
- DOT is standard of care
- Check bacteriologic response monthly
- HIV test
- Drug susceptibility vs. adherence for persistent cases
- “Never add a single drug to a failing regimen”

When are they non-infectious?

- On adequate therapy
- Clinical response
- 3 consecutive negative sputum smears from sputum collected on different days

Infection Control

- Administrative controls
  - Primary strategy for infection control! *****
  - “Develop policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB”
- Engineering controls (ventilation)
  - Isolation
  - Negative pressure rooms
- Personal respiratory protection (N95)

HIV and TB

- 10% risk of progression per year
- Leading cause of death in HIV patients
- MDR and XDR TB
- Drug interactions

MDR and XDR

- MDR=INH, RIF resistance
- XDR=MDR+
  - Any fluoroquinolone; **AND**
  - 1 of 3 injectable second line drugs
    - Capreomycin
    - Kanamycin
    - Amikacin

Latent TB Infection (LTBI)

- LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of TB disease.
- Estimated 4.2% of the US is infected with LTBI (11 million)

Bennett DE. *AJRCCM* 2008;177:348.

LTBI vs. Pulmonary TB Disease

Latent Tuberculosis Infection

- TST* or IGRA† positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease

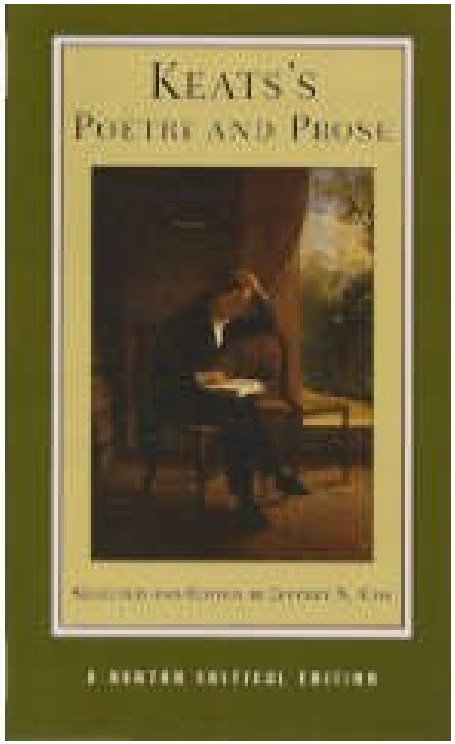
Pulmonary TB Disease

- TST or IGRA usually positive
- Chest radiograph may be abnormal
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens *may* be smear or culture positive

*** Tuberculin Skin Test (TST)**

† Interferon Gamma Release Assay (IGRA) are blood tests to detect *M. tuberculosis* infection.

TB Trivia 3



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Low-stress pretest: Question 2

- When you see a patient, what do you define as a positive TB skin test?
  a) 5 mm
  b) 10 mm
  c) 15 mm
  d) It depends on the epidemiological characteristics and degree of TB exposure of the patient

Table 7. Criteria for tuberculin positivity, by risk group

Reaction ≥5 mm of induration	Reaction ≥10 mm of induration	Reaction ≥15 mm of induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 yr) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees† of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)*	Mycobacteriology laboratory personnel	
	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk	

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19–34.

CDC. *MMWR* 2000;49:1-51.

Low-stress test: Question 3

- Do you treat every patient that has a positive PPD?

a) Yes

b) No

Decision to treat

- "A decision to test is a decision to treat"
  - Don't ignore a positive test
  - However, don't test low-risk populations!
- Must rule out active TB first
  - Symptoms of active TB
  - Chest x-ray
  - 3 sputum smears if symptoms
- Look at criteria to determine cutoff
- ***Assess risks & benefits for each individual patient***
  - Medical history (esp. liver disease, alcohol abuse)
  - Pregnancy
  - Allergies
  - How close and how recent was contact with active TB case

CDC Guidelines Call for Targeted Testing Only

- Targeted testing:
  - "…targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk." (MMWR 2000)
  - All military services conduct universal testing at accession
- CDC clearly considers high-risk:
  - Hospitals and health care settings (MMWR 2005)
  - Prisons (MMWR 2006)
  - HIV-infected, homeless, contacts of active case, etc. (MMWR 2000, 2005)
  - Military not considered high-risk

Testing for *M. tuberculosis* Infection

1. Mantoux tuberculin skin test (aka TST or PPD)

Skin test that produces delayed-type hypersensitivity reaction in persons with *M. tuberculosis* infection

2. Interferon Gamma Release Assays (IGRAs)

Blood tests that measure and compare amount of interferon-gamma (IFN-γ) released by blood cells in response to antigens.

Oxford Immunotec

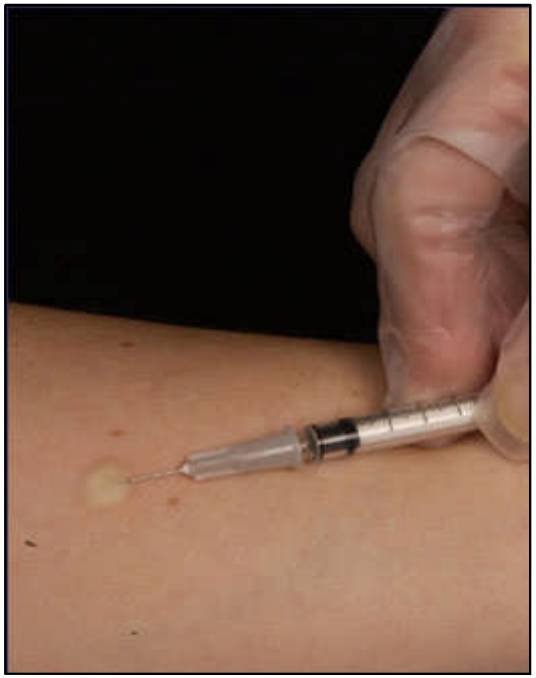
Harnessing the power of T cell measurement

The TB Skin Test

- Cell-free purified protein fraction extracts obtained from a human strain of *M. tuberculosis*
- History and significance
  - 100 years of use with known endpoints of active TB disease
- Problems with TST
  - ***Positive predictive value is low if prevalence of infection is low***
  - Errors and variability in administration
  - False negatives and false positives

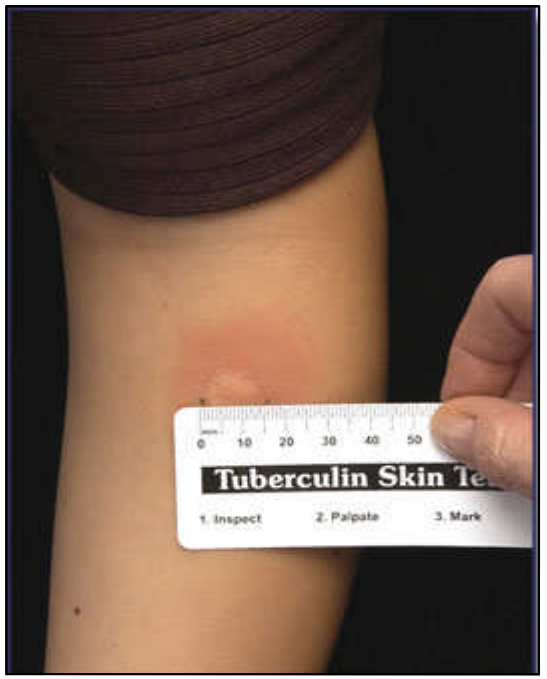
Administering the TST

- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produce a wheal 6 to 10 mm in diameter



Reading the TST

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema
- Record reaction in millimeters, not “negative” or “positive”
- Ensure trained health care professional measures and interprets the TST



Boosting and two-step testing

- Boosting
  - May have an initially negative test due to waning responsiveness
  - First test may stimulate immune response for second test
  - Second test positive=boosted reaction
- Two-step testing
  - Standard of care when doing repeated testing
  - Differentiates boosted reaction from recent infection
  - Patient is considered positive if 1st or 2nd test is positive

TB Trivia 5

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The Interferon Gamma Release Assay (IGRA)

- Measures interferon-gamma released from lymphocytes in whole blood samples incubated with antigens to MTB
  - ***Unknown progression of positives to active TB***
  - ***Better specificity, but concerns with sensitivity***
  - ***Lack of "gold standard"***

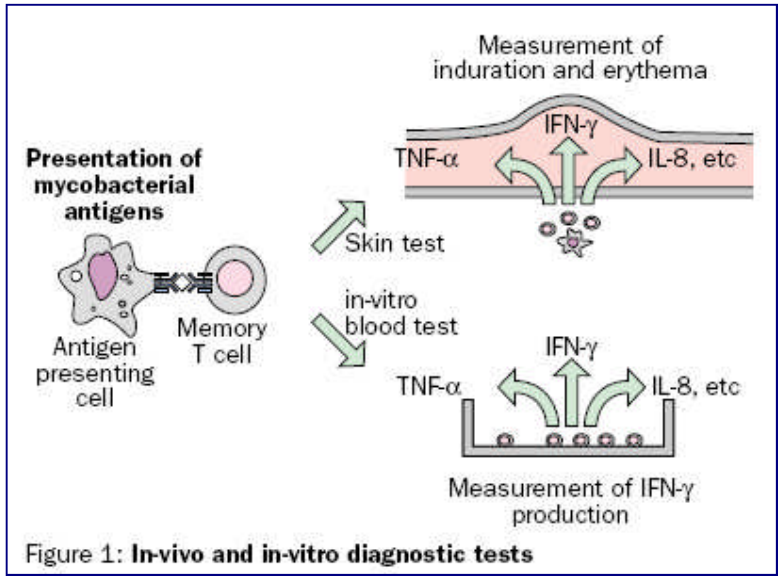


Figure 1: **In-vivo and in-vitro diagnostic tests**

Andersen P et al. *Lancet* 2000;356:1099.

When should I use the IGRA?

- Depends who you talk to
  - CDC guidelines: may be used to replace TST, but don't do both
  - UK, many other European countries: use IGRA as confirmatory test
  - Military policies conform with CDC, but Navy Great Lakes is using it as a confirmatory test
- Evolving issue, not resolved yet
  - More data
  - Evolving technology

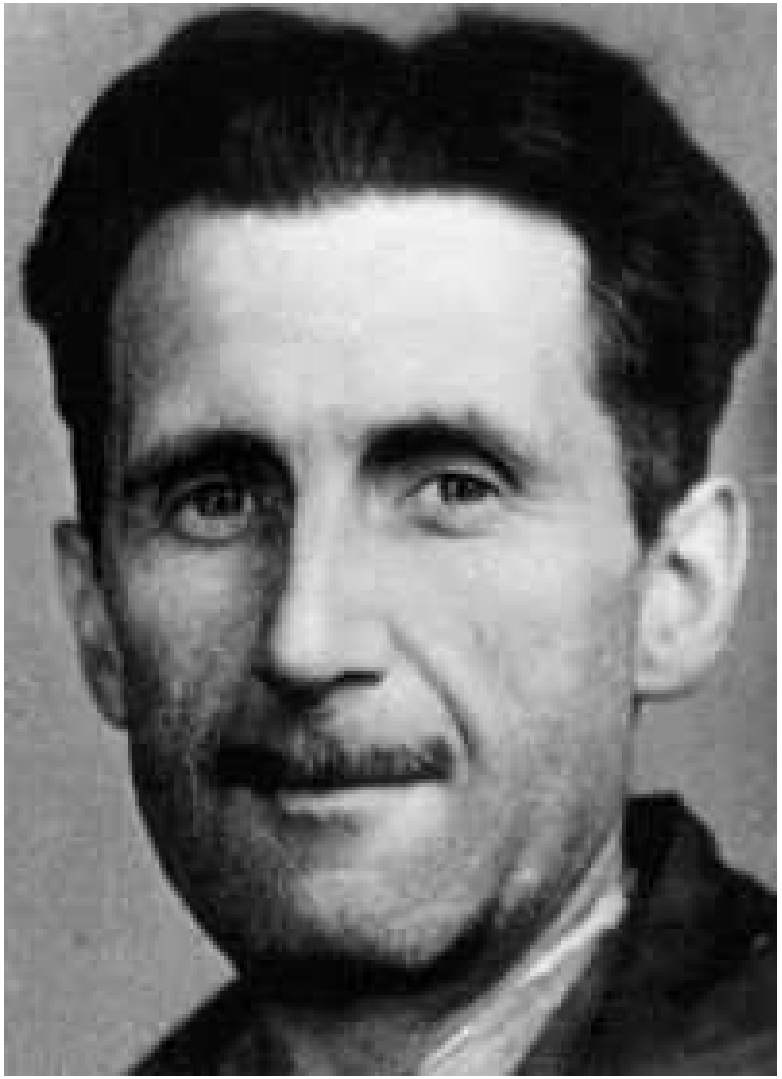
Pros of IGRAs

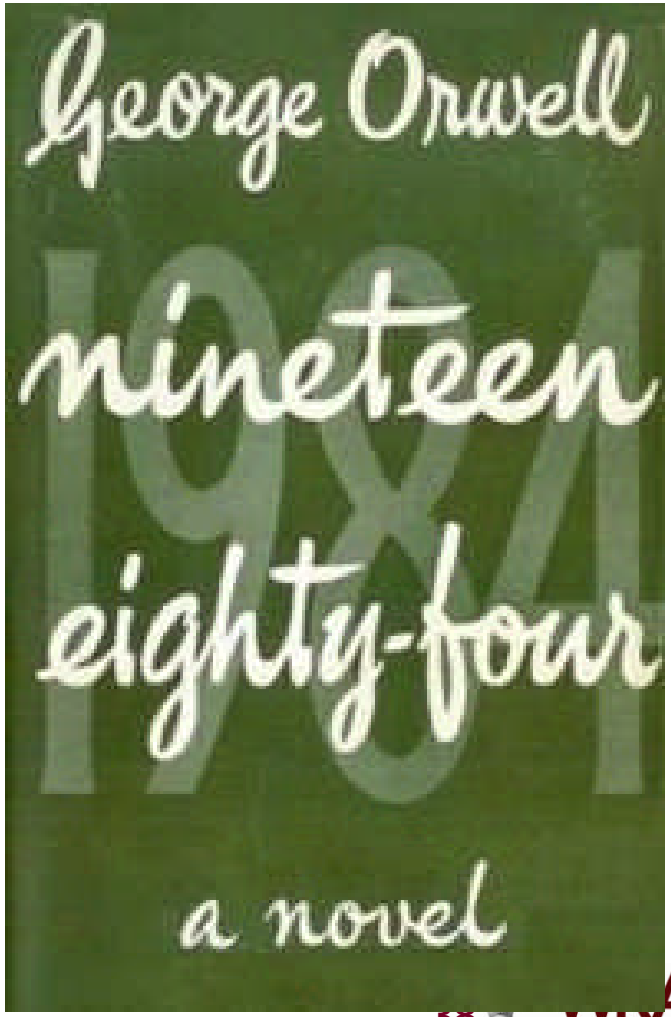
- Logistically easier FOR MEDICAL STAFF
- Minimize errors in skin test administration (QA/QC of TST)
- No follow-up visit
- Probably have better specificity (less false positives)
- May not have boost effect

Cons of IGRAs

- Logistically harder FOR LAB STAFF
- Increases overall budget
- Little data on progression to active TB (decades of data for TST)
  - Uncertain if sensitivity of test is as good as TST
- Hides sources of error by substituting clinical errors with lab errors
  - For example, indeterminate tests and samples with inconsistent results are common
  - Also, must be run in 8-12 hours after blood draw!

TB Trivia 6





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What do the US Military Services Do?

- Over 250,000 tests per year among recruits
- Accessions: all services do universal screening
  - Army (DA PAM 40-11; 20 Oct 2008)
  - Navy (BUMED Instruction 6224.8A; 12 Feb 2009)
  - Air Force (AFI 48-105; 1 Mar 2005)
- Prevalence of TST reactors
  - Navy: 5%
  - Army: 3%
  - Air Force: 1.5%
  - ***Depends on proportion of foreign-born***
- **Deployment-related screening**

Recent Deployment TB Epidemiology

- Outbreaks on Navy ships—common in the 1960s
  - USS Wasp (1998): 21 infected from failure to diagnose index case
  - USS Ronald Reagan (2003): 1 case reactivated despite prior INH Rx
- Active TB: lower rate of disease than in the US population
- TST reactors during deployment
  - Risk of TST conversion: about 1-2% per test
  - Problems with false positives and pseudo-outbreaks of TST conversions

Lamar. *Mil Med* 2003; 168(7):523-7.

CDC. *MMWR*. 2007;55:1381-2.

Camarca MM and Krauss MR. *Mil Med* 2001;166(5):452-6

Mancuso J. *AJRCCM* 2008:177:1285-9.

Potential sources of false-positive tuberculin skin test results

Product-related	Host factors	Administration	Cross-reactivity
Hot lots	HIV	Wrong reagent used (Td)	Non-tuberculous mycobacteria
Quality control	Biologic variability	Wrong amount used	BCG vaccine
Between-manufacturer variation (Aplisol)	Immunosuppression	Not administered correctly (intradermally)	
	Boosting	Not read correctly	
	Age	Not documented correctly	
		Intra-tester variation	
		Inter-tester variation	
		Losses to follow-up (previous positive test not read)	

Mancuso. *AJRCCM* 2008;177:1285-9.

Non-tuberculous Mycobacteria (NTM)

- Sensitization to NTM in the US is increasing
- Areas with high rates of TB may also have high rates of NTM
- Cross-reactivity causes false positives on PPD, especially if PPD <15 mm
- Major potential source of misclassification in military population

Khan K. *Am J Respir Crit Care Med.* 2007;176(3):306.

Von Reyn CF. *J Infect Dis.*1993;168(6):1553.

Von Reyn CF. *Int J Tuberc Lung Dis.* 2001;5(12):1122.

Margileth AM. *Mil Med.* Dec 1986;151(12):636.

What about guidelines for travelers?

- US Guidelines (CDC Yellow Book): both pre- and post-travel testing for those with "prolonged exposure to tuberculosis…e.g. [routine contact with] hospital, prison, and homeless shelter populations"
- IDSA Guidelines: TST "should be performed for those with anticipated exposure to TB or long-term stays in developing areas or when requested by the traveler because of concern about exposure"
- TRAVAX: "travelers to countries with high risk (i.e., > 100 cases per 100,000) should have pre-departure testing if staying for > 1 month; travelers to countries with moderate risk (approximately 25-100 cases per 100,000) should have pre-departure testing if they plan on staying for > 3 months"
- Canadian Guidelines: a single, post-travel test based on duration of travel as well as TB incidence in the country visited.

1. MF Iademarco. Tuberculosis. In: Health Information for International Travel 2008. Atlanta, GA: CDC, 2008.
2. Hill et al. *CID* 2006;43:1514.
3. Shoreland. Tuberculosis. Available at , Accessed 6 June 2009.

W Wobeser et al. Surveillance and screening in tuberculosis control. In: Canadian tuberculosis standards: Publi
Health Agency of Canada, 2007.

Hmmm…so what does the US military do for “travelers” (deployers)?

- Air Force moved to targeted testing after deployment in ’05 (AFI 48-105)
- Army
  - Used to test before deployment, after deployment, and then again 3-6 months after deployment (3 tests per deployment)
  - In 2008, moved to targeted testing after deployment using DD 2796 (OTSG Memo, 25 Sept 2008)
- Navy
  - Used to test operational units yearly with TST
  - Now targets testing during PHA with questionnaire (BUMEDINST 6224.8A, 12 Feb 2009)

Air Force

POST-DEPLOYMENT TUBERCULOSIS (TB) EXPOSURE RISK ASSESSMENT
SOURCE: Appendix 4, AFMS Deployment Health Surveillance Implementation Instructions, May 2003

1. Please answer the following questions to assist us in determining your risk for TB exposure during this recent deployment.

a. During this deployment, were you exposed to anyone known to have or suspected of having active TB (i.e., individuals with persistent cough, weight loss, night sweats and/or fever). YES____ NO____

b. During this deployment, did you have direct and prolonged contact with any individuals of the following groups: Refugees or Displaced Persons; Hospital, Prison, or Homeless Shelter Populations. YES NO

c. List the country(ies) where you were deployed to during this recent deployment:_____. During this deployment, did you have direct and prolonged contact with the local population (other than those listed in item b)? YES NO

STOP HERE

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2. **For Internal Use Only:** The decision to screen for tuberculosis (TB) is based on individual risk of exposure to TB. Therefore, deployment to high-prevalence* or high disease burden countries for 30 or more consecutive days is not by itself and indication for tuberculin skin testing.

a. Screen all members who answer "yes" to questions a or b, regardless of TB prevalence. For question c, screen if member answers "yes" and deployment was to a high TB prevalence country(ies).*

b. Air Force Institute of Operational Health (AFIOH) uses a variety of sources to determine high prevalence. Refer to the below link for each country's status: Https://afioh.brooks.af.mil/pestilence/. For direct link, see Country Risk Assessment

c. Members who require screening must have a tuberculin skin testing requirement entered in the current automated tracking system with a due date of 3 months after deployment and a mechanism must be in place to prompt members to return for testing when due.

Navy (NAVMED 6224/8, Aug 08)

INTERIM TUBERCULOSIS EXPOSURE RISK ASSESSMENT

FOR THE PATIENT *(Check the correct response)*

1. Since your last tuberculosis risk assessment, were you exposed to anyone known to have or suspected of having active tuberculosis (i.e., individuals with persistent cough, weight loss, night sweats, and/or fever)? ☐ YES ☐ NO ☐ DON'T KNOW

2. Since your last Tuberculosis Exposure Risk Assessment or Post-Deployment Health Assessment (DD Form 2796), did you have direct and prolonged contact with any individuals of the following groups: refugees or displaced persons; hospitalized patients, prisoners, or homeless shelter populations? ☐ YES ☐ NO

3. List any countries where you have traveled or deployed to since your last tuberculosis risk assessment.

4a. During this travel, did you have direct and prolonged contact with the local population? ☐ YES ☐ NO

4b. If yes, explain.

FOR THE PROVIDER

5. Tuberculosis risk assessment, based on above responses ☐ MINIMAL RISK ☐ INCREASED RISK

6. Recommend LTBI Testing ☐ YES ☐ NO

7. Provider Comments

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Army (DD 2796, Jan 2008)

From service member section, page 4:

20. This question assesses your personal risk for exposure to tuberculosis or other local infectious diseases. Would you say your INDOOR contact with local or 3rd country nationals was:

○ None ○ Minimal *(less than 1 hour per week)* ○ Moderate *(1 or more hours per week, but not daily)* ○ Extensive *(at least 1 hour per day, every day)*

From provider assessment section, page 6:

8. Tuberculosis risk assessment, based on response to question 20.
   - ○ Minimal risk
   - ○ Increased risk

   Recommend tuberculosis skin testing in 60-90 days ○ Yes ○ No

TB Trivia 7

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Low-stress test: Question 6

- Which of the following is the preferred first line drug combination to treat LTBI?
  a) Moxifloxacin for 3 months
  b) Rifampin and Pyrazinamide for 2 months
  c) Isoniazid for 9 months
  d) Rifampin for 4 months
  e) Isoniazid for 6 months

TABLE 4: Treatment Regimens

Drug/Dose	Frequency/Duration	Rating* (Evidence)† HIV negative	Rating* (Evidence)† HIV positive
Preferred Regimen			
Isoniazid Adult: 5 mg/kg Children: 10-20 mg/kg Maximum dose 300 mg	Daily x 9 months	A (II)	A (II)
Alternate Regimens			
Isoniazid Adult: 15 mg/kg Children: 20-40 mg/kg Maximum dose 900 mg	Twice weekly x 9 months§	B (II)	B (II)
Isoniazid Adults: 5 mg/kg Maximum dose 300 mg	Daily x 6 months	B (I)	C (I)
Isoniazid Adults: 15 mg/kg Maximum dose 900 mg	Twice weekly x 6 months§	B (II)	C (I)
Rifampin Adults: 10 mg/kg Children: 10-20 mg/kg Maximum dose 600 mg	Daily x 4 months	B (II)	B (II)

Note: A regimen of rifampin and pyrazinamide for the treatment of LTBI should generally not be offered due to risk of severe adverse events.

In situations in which rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

**Strength of the recommendation: A = preferred regimen; B = acceptable alternative; C = offer when A and B cannot be given*

† Quality of the supporting evidence: I = randomized clinical trials data; II = data from clinical trials not randomized or from other population

§ Intermittent regimen must be provided via directly observed therapy (DOT), i.e., health care worker observes the ingestion of medication

CDC. Guide for Primary Health Care Providers: Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. 2005.

LTBI Treatment Myths

- Must be under 35 years old to treat
  - Liver disease is the more important factor
- Patients with BCG vaccination should not be treated
  - 10 mm or greater reaction should be considered for therapy regardless of BCG
- Serial liver enzyme tests should be performed for all LTBI patients
  - Liver enzymes are not routinely done (see next slides)
  - Clinical monitoring monthly
- 6 month therapy is the standard regimen

Patient Instructions

No alcohol!

Instruct patient to report signs or symptoms of adverse drug reactions:

- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet

Monthly Clinical Monitoring

Monthly visits should include a brief physical exam and a review of

- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment

Baseline Laboratory Monitoring

Baseline liver function tests (e.g., AST, ALT, and bilirubin) are not necessary except for patients with the following risk factors:

- **HIV infection**
- **History of liver disease**
- **Alcoholism**
- **Pregnancy or in early postpartum period**

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Continued Laboratory Monitoring

Repeat laboratory monitoring if patient has:

- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during examination

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Adverse Effects of Medications: Isoniazid (INH)

- 10-20% have elevated liver enzymes
  - Up to 5 times normal
  - Usually return to normal even if rx is continued
- Clinical hepatitis in 0.1%
- Peripheral neuropathy in 0.2%
  - More common with liver disease, diabetes
  - Rx with Vitamin B6 (Pyridoxine)

Adverse Effects of Medications: Rifampin (RIF)

- Hepatotoxicity in 0.6%
- Cutaneous reactions in 6%
- GI symptoms rarely severe
- Orange discoloration of body fluids
- Drug interactions (warfarin, OCPs, phenytoin)
- Contraindicated in HIV-infected individuals on certain PIs or NNRTIs
  - Substitute with Rifabutin

Adherence

- LTBI therapy not compulsory (active TB is)
- Adherence is abysmal (up to 50% complete therapy)
  - Therapeutic alliance
  - Don't treat (or test!) low-risk patients
- Ways to improve adherence
  - Improve access for patient
  - Good information and education
  - 270 doses in 365 days for INH
  - Alternate regimens (intermittent, RIF)
  - Ensure continuity of care through PCS
    - Treat as soon as possible (during deployments, in basic training)

Who handles these cases?

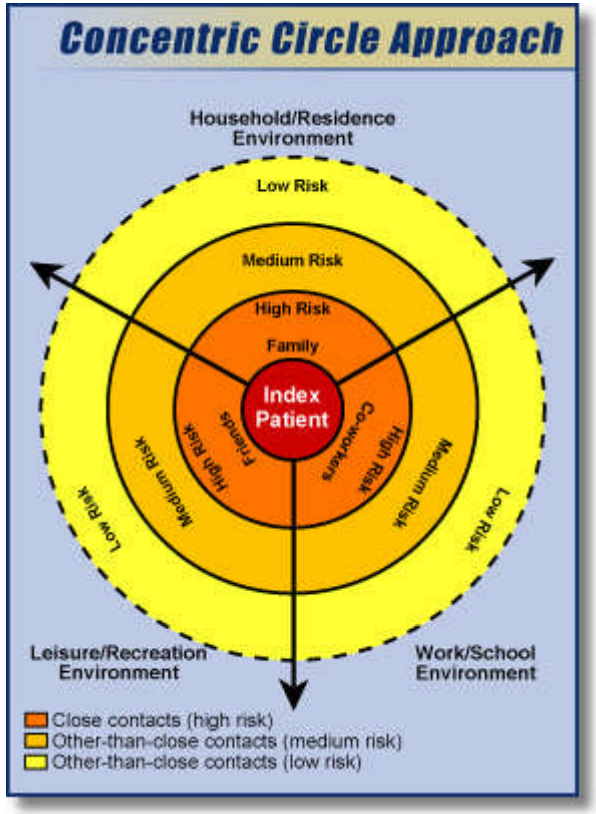
- Civilian: public health/primary care partnership
  - Most county health departments offer therapy free of charge
- Military: Usually referred to Preventive Medicine
  - Can be ID, pulmonology, or primary care
  - Public health nurses usually do monthly clinical follow-up
- In the field (e.g. predeployment test is positive)
  - Many elect to defer therapy until after deployment
  - Depends on comfort level, available resources, and closeness of contact

Other LTBI Testing Issues

- Must maintain good quality testing program, whether TST or IGRA
  - Both are difficult in the field
    - Should only be performed for contact investigations
  - Useful QA/QC guidelines for TST quality control in Appendix F of: CDC.*MMWR* 2005;54(RR-17):138-9.
- Tubersol is the only TST that should be used
  - False positives with Aplisol
  - HA Policy 08-012 (29 Sept 08)

Contact Investigations

- Concentric circles of contacts
- Need to retest 8-10 weeks after last contact with case
- Garrison
  - Refer to Preventive Medicine
  - CDC.*MMWR* 2005;54(RR-15).
- Deployment
  - Refer to Preventive Medicine
  - Policy guidance: MNCI. Tuberculosis Prevention and Control Policy; 26 Mar 2008.



WRAIR
Walter Reed Army Institute of Research
Soldier Health • World Health

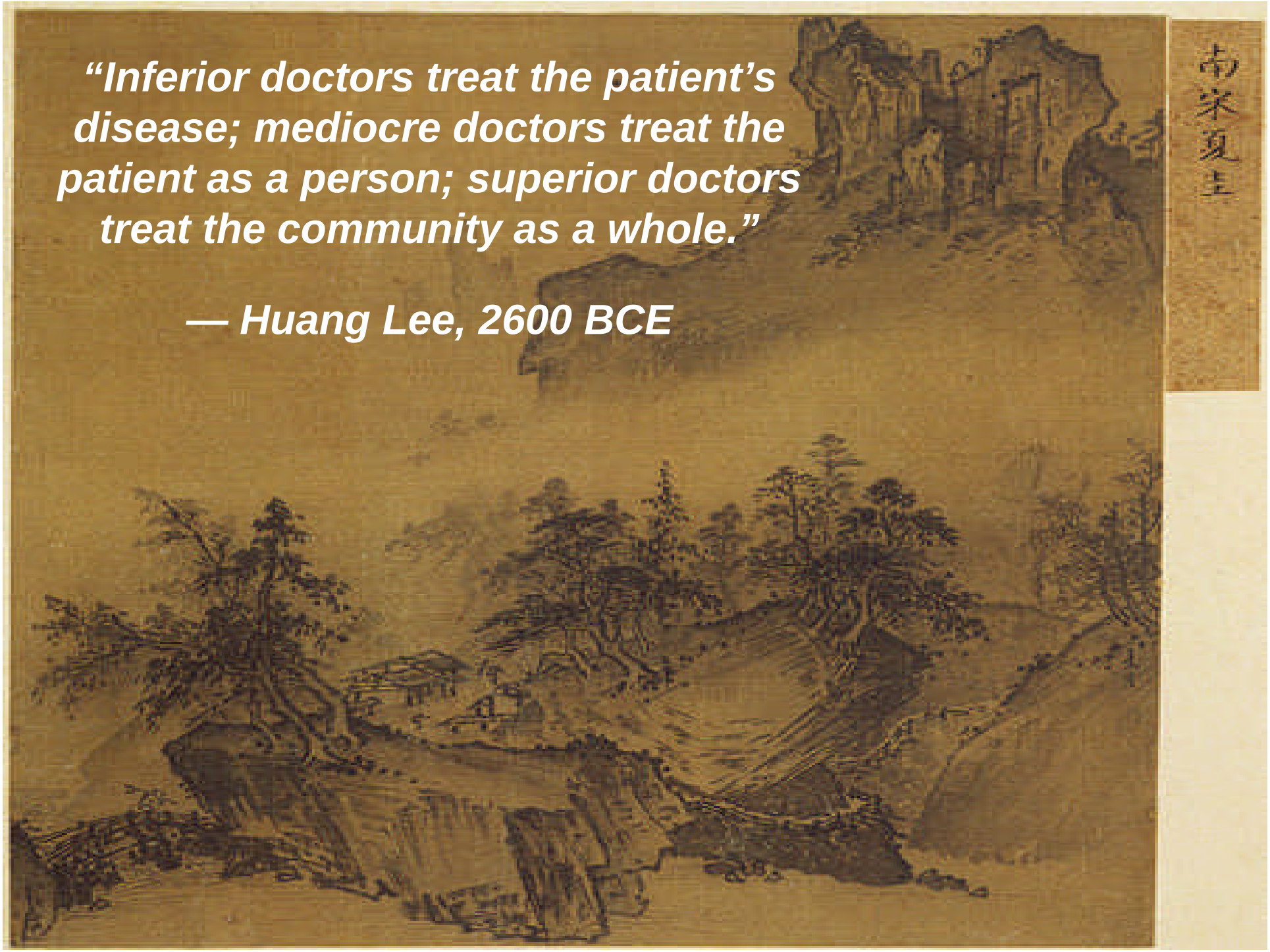
BCG

- Most common vaccination worldwide
- Controversial effectiveness in the US
  - Most solid: TB meningitis in children
- Leaves scar similar to vaccinia (smallpox vaccine)
- Cross-reactivity to TST but not IGRA
- Almost never given in US citizens

Other important management issues

- Directly observed therapy (DOT)
  - Standard of care for Active TB
  - May be used for LTBI, but uncommon
  - Refer to Preventive Medicine
- Disease reporting
  - Active TB is a reportable disease, LTBI is not
  - Positive TST or IGRA must be documented in an electronic registry (ALTHA, MEDPROS, etc)
  - Reportable diseases are reported to Preventive Medicine both in Garrison ***and Deployment***

TB Trivia 8



“Inferior doctors treat the patient’s disease; mediocre doctors treat the patient as a person; superior doctors treat the community as a whole.”

— Huang Lee, 2600 BCE